REMARKS/ARGUMENTS

Claims 23-28, 40-52 and 64-73 are pending in this application. Claims 23, 42, 47, and 71 have been amended. The amendments are of formal nature and are fully supported by the specification as originally filed. All amendments were made without prejudice or disclaimer. Applicants explicitly reserve the right to pursue any deleted subject matter in one or more continuing applications.

Interview Summary

On November 10, 2009, the undersigned attorney contacted Examiner Holleran to point out the contradiction between the Office Action Summary which indicates that the Office Action mailed on May 14, 2009 is non-final, and the statement that "THIS ACTION IS MADE FINAL" on page 14. The Examiner indicated the Patent Office records would be corrected to clearly indicate that the Office Action is non-final.

Information Disclosure Statement

The Examiner did not consider the Miller et al. reference originally submitted with the Information Disclosure Statement submitted on August 24, 2007, because the citation lacked a publication date. This reference is resubmitted with a Supplemental Information Disclosure Statement accompanying the present response, including the publication date. The supplemental Information Disclosure Statement additionally cites US Publication No. 2009/0081223 and US Patent 7,449,184, which are related to the present application.

Prior Rejections

Applicants note and appreciate withdrawal of the earlier rejections under 35 U.S.C. § 112, second and first paragraphs, 35 U.S.C. § 102, and 35 U.S.C. § 103 as discussed on pages 2-4 of the present Office Action.

New Grounds of Rejection:

I. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 23-28, 40-52, 64-73 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the rejection, claims 23, 47 and 71 are indefinite because the stated purpose of each of the methods does not correlate with the steps set forth. Claim 42 is held indefinite because the phrase "the tumor" allegedly lacks antecedent basis in claim 23 from which claim 42 depends.

The current amendments of claims 23, 42, 47, and 71 are believed to obviate this rejection, the withdrawal of which is respectfully requested.

II. Claim Rejections Under 35 U.S.C. §103

(1) Claims 47-52, 64 and 66-70 are rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Sliwkowski (U.S. 6,949,245; issued Sep. 27, 2005; effective filing date is June 25, 1999) in view of Bangalore (Bangalore, L., et al. Proc. Natl. Acad. Sci, USA, 89: 11637-11641, 1992) or DiGiovanna (Giovanna, M. P. et al. Cancer Research 55:1946-1955, 1995).

Sliwkowski is cited for its teaching of a method to treat a subject with an anti-HER2 antibody, rhuMAb 2C4 where the subject has a cancer that may be characterized as having excessive activation of an ErbB receptor.

Bangalore is cited for allegedly teaching a method of measuring phosphorylated ErbB2 (HER2), and that such a measurement would be useful to measure ErbB2 activation levels directly on biopsy specimens. The Examiner further refers to page 11637, left column as allegedly teaching that receptor activity may be a better prognostic indicator than ErbB2 amount.

DiGiovanna is cited for allegedly teaching the use of immunohistochemistry on formalin-fixed and paraffin-embedded surgical specimens from human breast tumors using an antibody that is specific for phosphorylated HER2. DiGiovanna is further cited as allegedly teaching that the extent of HER2 tyrosine phosphorylation varies considerably and that it is likely that measurement of HER2 signaling activity, as opposed to HER2 abundance, will greatly enhance methods that use detection of HER2 for prognosis and treatment decisions, and that tumors most vulnerable to anti-HER2 antibodies will be those that are dependent on HER2 signaling for growth.

According to the rejection, it "would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sliwkowski with those of Bangalore or DiGiovanna to make the claimed methods, because Sliwkowski teaches a method for the treatment of cancers where an ErbB receptor is activated and Bangalore or DiGiovanna teaches that phosphorylation of Her2 is a measurement of Her2 signalling activity." (Office Action, page 9, first paragraph)

Applicants disagree and respectfully traverse the rejection.

The invention claimed in the present application uses the detection of ErbB receptor phosphorylation to identify a HER2-positive tumor as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family.

Sliwkowski discloses the use of an ErbB2 antibody, rhuMAb 2C4, which inhibits heregulin (HRG) dependent association of ErbB2 with ErbB3. The teaching relied on from Bangalore does not address the issue of responsiveness to such antibodies, or, for that matter, to any kind of cancer treatment.

While Bangalore makes a general suggestion that the extent of tyrosine phosphorylation is a good indicator of receptor activity, it correlates receptor activity with overall prognosis of a cancer patient and not with response to any treatment, such as treatment with any particular antibody, e.g. an anti-ErbB2 antibody inhibiting the association of HER2 with another member

of the ErbB family. Thus, the combination of Sliwkowski with Bangalore has no teaching whatsoever about using the detection of ErbB receptor phosphorylation as a means to predict patient response to cancer treatment, in particular to treatment with an antibody inhibiting association of HER2 with another member of the ErbB receptor family.

DiGiovanna suggests, in generic terms, that detecting phosphorylation of the p185 (ErbB2) receptor might be used to predict responses to anti-p185 (anti-ErbB2) immunotherapy. However, DiGiovanna provides absolutely no evidence that this would be the case, or that this tentative suggestion might apply to the type of antibodies which inhibit the association of HER2 with another member of the ErbB receptor family. In view of the known high degree of unpredictability in the field of cancer therapy, the combination of the disclosures of Sliwkowski and DiGiovanna does not create a reasonable expectation that tumor/patient response could be predicted based on detecting HER2 phosphorylation.

In conclusion, the combination of Sliwkowski with Bangalore or DiGiovanna, as cited in the present rejection, does not make obvious the invention claimed in claims 47-52, 64, and 66-70, and the present rejection should be withdrawn.

(2) Claims 47-52, 65-73 are rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Sliwkowski (U.S. 6,949,245; issued Sep. 27, 2005; effective filing date is June 25, 1999) in view of Bangalore (Bangalore, L., et al. Proc. Natl. Acad. Sci, USA, 89: 11637-11641, 1992) or DiGiovanna (supra). The reasoning explaining the rejection additionally relies on Terstappen (US 6,365,362), which is not listed as part of the combination of references on which the present rejection is based. Applicants assume that it was the Examiner's intention to list Terstappen in combination with Sliwkowski and Bangalore or Sliwkowski and DiGiovanna, and will address the present rejection accordingly.

Sliwkowski, Bangalore and DiGiovanna are relied on for the same disclosure as that cited in support of the previous rejection. Terstappen is cited for the teaching that carcinoma cells in the blood may be assayed immunocytochemically to characterize the circulating tumor cells, and that such methods may be used to monitor patients for recurrence of cancer or for response to

therapy. The Examiner adds that Terstappen also teaches that levels of tumor markers such as Her2 may be assessed.

According to the rejection, "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified Bangalore or DiGiovanna's method so that it could be used in the measurement of Her2 phosphorylation status of circulating tumor cells." (Office Action, page 11, last paragraph)

The rejection is respectfully traversed.

Without acquiescing to the rejection, or the Examiner's analysis based on Terstappen, Applicants submit that, as explained in response to the previous rejection, the claims are not rendered obvious by the combination of Sliwkowski and Bangalore or Sliwkowski and DiGiovanna. The addition of Terstappen to the cited combination does not change this outcome. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(3) Claims 23-28, 40 and 42-45 are rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Bangalore (supra) in view of DiGiovanna (supra), and further in view of Lewis (Lewis, G. D., et al., Cancer Research, 56:1457-1465, 1996).

Bangalore and DiGiovanna are cited as in support of the previous rejections. Lewis is cited for disclosing that monoclonal antibody 2C4 inhibits tyrosine phosphorylation due to heregulin addition to human breast and ovarian tumor cells. Thus, Lewis is cited for the alleged teaching that 2C4 is an antibody that blocks activation of HER2. According to the rejection, "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have tested the activity of rhuMAb2C4 on samples of tumor cells that exhibited activated ErbB2 . . . [and one] would have been motivated to combine the teachings of Bangalore, DiGiovanna and Lewis to make a method that tests the efficacy of rhuMAb2C4 on a patient's tumor sample to decrease phosphorylation of an ErbB receptor." (Office Action, page 13, 3rd full paragraph)

The rejection is respectfully traversed.

Bangalore and DiGiovanna, when taken alone or in combination, do not teach a method of identifying a HER2 positive tumor as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family based on phosphorylation of the HER2 receptor, with a reasonable expectation of success. The fact that Lewis teaches that 2C4 inhibits tyrosine phosphorylation and blocks activation of HER2 does change this conclusion. Accordingly, the present rejection is believed to be misplaced and should be withdrawn.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned agent at the telephone number shown below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **50-4634** (referencing Attorney's Docket No. **GNE-0114 US (123851-181770)**).

Respectfully submitted,

Date: November 13, 2009

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